

Supplementary Online Content

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eTable 1. Effects of Each MS-Associated HLA Allele and SNP on the MS Phenotypes Nominally Correlated With HLAGB

eTable 2. Association Between HLAGB and MS Phenotypes

eTable 3. Standardized Coefficients of MRI Parameters in Lasso Model for Each Gender Data Set

eTable 4. Association of Common *HLA-DRB1*15:01* Haplotypes With MS

eTable 5. Effect of Each MS-Associated *HLA-DRB1*15:01* Haplotype on the Subcortical Gray Matter Fraction in Female MS

eTable 6. Association Between HLAGB and MS Phenotypes in a Combined Study of Both Gender Data Sets

eFigure 1. Survival Analysis of Conversion Timing From Clinically Isolated Syndrome to Clinically Definite Multiple Sclerosis

eFigure 2. Standardized Coefficients of MRI Parameters in Lasso Model for Each Gender Data Set

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Effects of Each MS-Associated HLA Allele and SNP on the MS Phenotypes Nominally Correlated With HLAGB

Phenotype Category	Clinical			Brain MRI						Cervical Cord MRI		
Phenotype	Age at Onset			Cerebral White Matter Fraction			Subcortical Gray Matter Fraction			Gray Matter Area – UCCA ratio		
Patients Group	Female MS			Female MS			Female MS			Male MS		
	std. β	t value	P	std. β	t value	P	std. β	t value	P	std. β	t value	P
<i>HLA-DRB1*15:01</i> (trend)	-1.19 $\times 10^{-1}$	-2.41	1.7 $\times 10^{-2}$	-9.05 $\times 10^{-2}$	-1.91	5.7 $\times 10^{-2}$	-1.35 $\times 10^{-1}$	-2.98	3.0 $\times 10^{-3}$	-3.01 $\times 10^{-1}$	-2.07	4.5 $\times 10^{-2}$
<i>HLA-DRB1*03:01</i> (rec.)	4.65 $\times 10^{-2}$	0.93	3.5 $\times 10^{-1}$	-2.36 $\times 10^{-2}$	-0.50	6.2 $\times 10^{-1}$	-8.02 $\times 10^{-2}$	-1.78	7.6 $\times 10^{-2}$	1.69 $\times 10^{-1}$	1.12	2.7 $\times 10^{-1}$
<i>HLA-B*44:02</i> (trend)	5.58 $\times 10^{-2}$	1.12	2.7 $\times 10^{-1}$	4.78 $\times 10^{-2}$	1.01	3.1 $\times 10^{-1}$	9.52 $\times 10^{-2}$	2.11	3.6 $\times 10^{-2}$	-2.88 $\times 10^{-1}$	-1.97	5.5 $\times 10^{-2}$
<i>HLA-B*38:01</i> (trend)	7.55 $\times 10^{-2}$	1.51	1.3 $\times 10^{-1}$	6.21 $\times 10^{-2}$	1.31	1.9 $\times 10^{-1}$	-1.11 $\times 10^{-3}$	-0.02	9.8 $\times 10^{-1}$	1.91 $\times 10^{-1}$	1.28	2.1 $\times 10^{-1}$
<i>HLA-A*02:01</i> (dom.)	-2.97 $\times 10^{-3}$	-0.06	9.5 $\times 10^{-1}$	-8.84 $\times 10^{-2}$	-1.87	6.2 $\times 10^{-2}$	3.36 $\times 10^{-2}$	0.74	4.6 $\times 10^{-1}$	-2.47 $\times 10^{-1}$	-1.67	1.0 $\times 10^{-1}$
rs9277565_T (trend)	2.15 $\times 10^{-2}$	0.43	6.7 $\times 10^{-1}$	3.63 $\times 10^{-2}$	0.77	4.4 $\times 10^{-1}$	5.16 $\times 10^{-2}$	1.14	2.5 $\times 10^{-1}$	-2.78 $\times 10^{-2}$	-0.18	8.6 $\times 10^{-1}$
<i>HLA-DQB1*03:02</i> (dom.)	4.46 $\times 10^{-2}$	0.89	3.7 $\times 10^{-1}$	-2.00 $\times 10^{-2}$	-0.42	6.7 $\times 10^{-1}$	1.63 $\times 10^{-3}$	0.04	9.7 $\times 10^{-1}$	-1.40 $\times 10^{-1}$	-0.93	3.6 $\times 10^{-1}$

Abbreviations: dom., dominant; HLAGB, human leukocyte antigen genetic burden; MS, multiple sclerosis; rec., recessive; SNP, single nucleotide polymorphism; std., standard; UCCA, upper cervical cord area.

eTable 2. Association Between HLAGB and MS Phenotypes

Phenotype	Baseline						Year 1					
	Female MS (n=393)			Male MS (n=178)			Female MS (n=367)			Male MS (n=168)		
	std. β	t value	P	std. β	t value	P	std. β	t value	P	std. β	t value	P
Cortical Gray Matter Fraction	-5.32 × 10 ⁻²	-1.22	2.2 × 10 ⁻¹	3.59 × 10 ⁻²	0.50	6.2 × 10 ⁻¹	-7.42 × 10 ⁻²	-1.61	1.1 × 10 ⁻¹	5.93 × 10 ⁻³	0.08	9.4 × 10 ⁻¹
Cerebral White Matter Fraction	-1.01 × 10 ⁻¹	-2.12	3.5 × 10 ⁻²	4.24 × 10 ⁻²	0.57	5.7 × 10 ⁻¹	-1.10 × 10 ⁻¹	-2.26	2.4 × 10 ⁻²	2.92 × 10 ⁻²	0.38	7.0 × 10 ⁻¹
Subcortical Gray Matter Fraction	-1.67 × 10 ⁻¹	-3.72	2.3 × 10⁻⁴	-2.42 × 10 ⁻²	-0.35	7.3 × 10 ⁻¹	-1.33 × 10 ⁻¹	-2.86	4.5 × 10⁻³	-2.35 × 10 ⁻²	-0.32	7.5 × 10 ⁻¹

Abbreviations: HLAGB, human leukocyte antigen genetic burden; MS, multiple sclerosis; MSSS, multiple sclerosis severity score (see Methods, Study Participants); std., standard.

eTable 3. Standardized Coefficients of MRI Parameters in Lasso Model for Each Gender Data Set

MRI type	MRI parameter	Female MS			Male MS		
		HLAGB	Age at Exam	Disease Duration	HLAGB	Age at Exam	Disease Duration
Brain	Cortical Gray Matter Fraction (BL)	-1.12 × 10 ⁻³	-2.98 × 10 ⁻¹	-1.59 × 10 ⁻¹	—	—	-4.81 × 10 ⁻²
	Cerebral White Matter Fraction (BL)	-3.40 × 10 ⁻³	3.66 × 10 ⁻²	-2.82 × 10 ⁻¹	—	—	-4.47 × 10 ⁻²
	Subcortical Gray Matter Fraction (BL)	-5.02 × 10 ⁻³	-1.74 × 10 ⁻¹	-2.50 × 10 ⁻¹	—	—	-7.13 × 10 ⁻²
	Lesion Volume ^a (BL)	2.72 × 10 ⁻³	-5.76 × 10 ⁻³	2.29 × 10 ⁻¹	—	—	6.14 × 10 ⁻²
Spinal Cord	Gray Matter Area	—	—	—	—	-6.95 × 10 ⁻²	-2.09 × 10 ⁻¹
	White Matter Area	—	—	—	—	-1.30 × 10 ⁻¹	-2.86 × 10 ⁻¹
	UCCA	—	—	—	—	-1.22 × 10 ⁻¹	-2.85 × 10 ⁻¹
	Gray Matter Area - UCCA ratio	—	—	—	—	4.27 × 10 ⁻²	1.93 × 10 ⁻²

Abbreviations: BL, baseline; HLAGB, human leukocyte antigen genetic burden; MS, multiple sclerosis; UCCA, upper cervical cord area.

^aNatural logarithm of lesion volume was taken to be normally distributed in the model.

eTable 4. Association of Common *HLA-DRB1*15:01* Haplotypes With MS

HLA-A-B-DRB1*15:01 haplotype	Whole MS					Bout-onset MS				
	Allele Frequency		OR	95% CI	<i>P</i>	Allele Frequency		OR	95% CI	<i>P</i>
	Cases	Controls				Cases	Controls			
A*03:01-B*07:02-DRB1*15:01	0.069	0.028	2.87	1.77 - 4.66	1.8 x 10⁻⁵	0.070	0.028	2.89	1.78 - 4.69	1.7 x 10⁻⁵
A*02:01-B*07:02-DRB1*15:01	0.027	0.015	1.97	0.99 - 3.94	5.4 x 10⁻²	0.028	0.015	2.06	1.03 - 4.11	4.1 x 10⁻²
A*24:02-B*07:02-DRB1*15:01	0.017	0.004	4.80	1.45 - 15.96	1.0 x 10⁻²	0.016	0.004	4.54	1.37 - 15.04	1.3 x 10⁻²
A*25:01-B*18:01-DRB1*15:01	0.016	0.004	3.93	1.24 - 12.44	2.0 x 10⁻²	0.016	0.004	4.09	1.29 - 12.94	1.7 x 10⁻²
A*X-B*X-DRB1*15:01 ^a	0.131	0.042	3.67	2.50 - 5.39	3.3 x 10⁻¹¹	0.133	0.042	3.75	2.55 - 5.51	1.8 x 10⁻¹¹

Abbreviations: CI, confidence interval; HLA, human leukocyte antigen; MS, multiple sclerosis; OR, odds ratio.

^aThe X refers to all other alleles than the alleles in the four DRB1*15:01 haplotypes shown above the dashed line.

eTable 5. Effect of Each MS-Associated *HLA-DRB1*15:01* Haplotype on the Subcortical Gray Matter Fraction in Female MS

<i>HLA-A-B-DRB1*15:01</i> haplotype	std. β	std. SE	95% CI	P
<i>A*03:01-B*07:02-DRB1*15:01</i>	-8.15×10^{-2}	4.57×10^{-2}	-0.17 — 0.01	7.4×10^{-2}
<i>A*02:01-B*07:02-DRB1*15:01</i>	8.56×10^{-3}	4.59×10^{-2}	-0.08 — 0.10	8.5×10^{-1}
<i>A*24:02-B*07:02-DRB1*15:01</i>	-1.28×10^{-1}	4.53×10^{-2}	-0.22 — -0.04	5.1×10^{-3}
<i>A*25:01-B*18:01-DRB1*15:01</i>	-5.95×10^{-2}	4.62×10^{-2}	-0.15 — 0.03	2.0×10^{-1}
<i>A*X-B*X-DRB1*15:01</i> ^a	-6.39×10^{-2}	4.58×10^{-2}	-0.15 — 0.03	1.6×10^{-1}

Abbreviations: HLAGB, human leukocyte antigen genetic burden; MS, multiple sclerosis; SE, standard error; std., standard.

^aThe X refers to all other alleles than the alleles in the four *DRB1*15:01* haplotypes shown above the dashed line.

eTable 6. Association Between HLAGB and MS Phenotypes in a Combined Study of Both Gender Data Sets

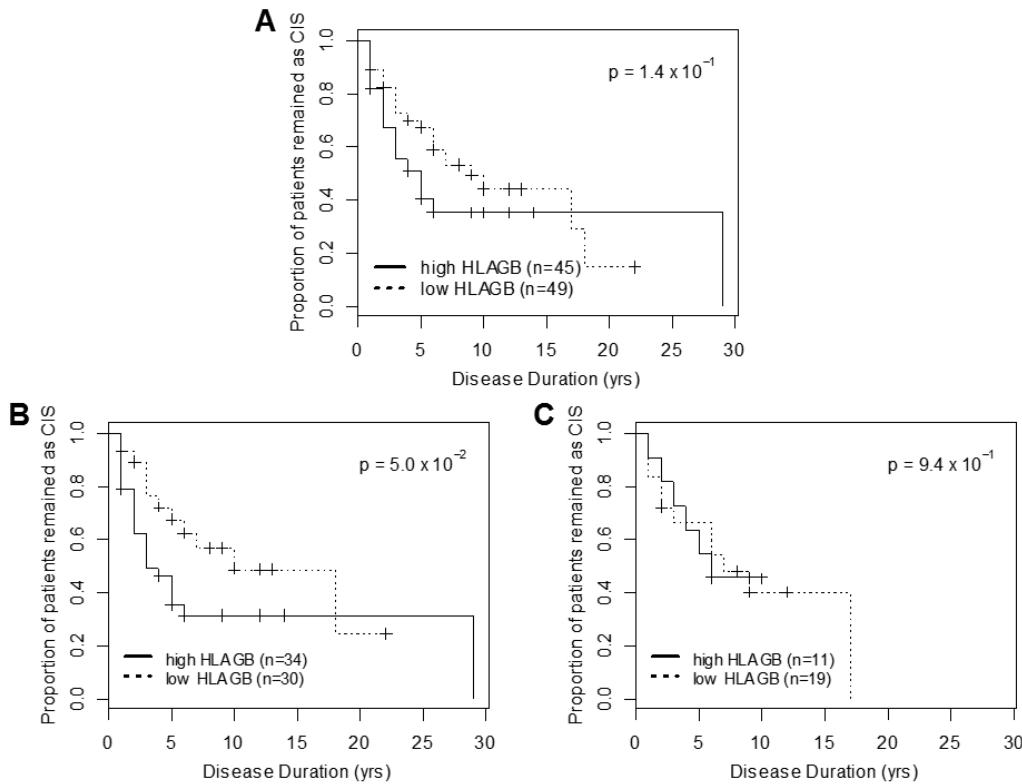
Parameter Category	Phenotype	std. β	t value	P
Clinical	Age at Onset	-8.11 x 10 ⁻²	-1.93	5.5 x 10 ⁻²
	MSSS ^a	-4.46 x 10 ⁻²	-1.06	2.9 x 10 ⁻¹
Brain MRI	Cortical Gray Matter Fraction (BL)	-1.30 x 10 ⁻²	-0.35	7.3 x 10 ⁻¹
	Cerebral White Matter Fraction (BL)	-5.40 x 10 ⁻²	-1.35	1.8 x 10 ⁻¹
	Subcortical Gray Matter Fraction (BL)	-1.02 x 10 ⁻¹	-2.68	7.6 x 10⁻³
	Lesion Volume (BL)	6.11 x 10 ⁻²	1.52	1.3 x 10 ⁻¹
Cervical Cord MRI	Gray Matter Area	-1.67 x 10 ⁻¹	-1.94	5.5 x 10 ⁻²
	White Matter Area	3.90 x 10 ⁻²	0.46	6.5 x 10 ⁻¹
	Whole Cord Area	-1.59 x 10 ⁻²	-0.19	8.5 x 10 ⁻¹
	Gray Matter Area - UCCA ratio	-2.32 x 10 ⁻¹	-2.49	1.4 x 10 ⁻²

Abbreviations: BL, baseline; HLAGB, human leukocyte antigen genetic burden; MRI, magnetic resonance imaging; MSSS, multiple sclerosis severity score (see Methods, Study Participants); std., standard; UCCA, upper cervical cord area.

^aMSSS was squared to be normally distributed in the model.

eFigure 1. Survival Analysis of Conversion Timing From Clinically Isolated Syndrome to Clinically Definite Multiple Sclerosis

The patients with clinically isolated syndrome (CIS) were divided into two groups by whether the HLAGB scores were higher than the median values of the whole patients or not (high/low HLAGB) and were assessed for the time to convert to clinically definite multiple sclerosis. (A) The whole CIS patients. (B) The female CIS patients. (C) The male CIS patients.



**eFigure 2. Standardized Coefficients of MRI Parameters in Lasso Model
for Each Gender Data Set**

The heatmap shows standardized coefficients (standard β) of HLAGB, age at examination (AAE), and disease duration (DD) on x-axis for each brain MRI parameter (y-axis). Multi-response lasso regressions were fit separately for female patients (above the black line, F) and male patients (below the line, M). GMF, gray matter fraction; WMF, white matter fraction; LesionV, lesion volume.

